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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,711	02/27/2007	Kara Calhoun	STAN-337	4793

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

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02/18/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,711	CALHOUN ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 10-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This Office Action is in response to the Applicant's reply received 12/13/10. Claims 1-6 and 10-19 are pending. No Claims are withdrawn. Claims 1-6 and 10-19 are considered on the merits.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6 depends from claim 1. Claim 1 includes three classes of "phosphates": nucleoside monophosphates, exogenous nucleoside triphosphates and exogenous phosphates. Claims 5 and 6 simply limit the generic "phosphate" but do not clearly identify which of the three phosphate classes is limited or if this is to limit all three classes combined. Clarification is required.

Claims 12 and 13 contain the limitation of "biological macromolecules" that do not have explicit basis in independent claim 1. Furthermore this limitation does not further limit claim 1. Biological macromolecules can read on lipid membranes, cellulose or other polysaccharides that are not encompassed in the scope of claim 1 which is drawn to polynucleotides and polypeptides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6 and 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swartz #1 (U.S. Patent # 6168931, issued 2001, in PTO-892, 9/22/10) in view of Schulte et al. (U.S. Patent Application # 2003/0113778, priority date 10/30/01).

These claims are drawn to a method of synthesizing polynucleotides and/or polypeptides in a cell-free reaction mix comprising:

- Bacterial cell extract;
- A template for the production of the polynucleotides and/or polypeptide;
- Monomers for the polynucleotides and/or polypeptides to be synthesized;
- Cofactors, enzymes and other reagents necessary for synthesis;
- At least 10mM of a phosphate free energy source that may include glutamate or pyruvate;
- Absence of exogenous **nucleotide triphosphates** (**NTPs**);
- At least 1mM of exogenous phosphate that is provided by potassium phosphate, magnesium phosphate or ammonium phosphate.

The phosphates such as potassium phosphate are further limited to a concentration of 1 mM to about 20 mM. Claim 7 limits that the phosphate source is released during the reaction. Claim 8 limits that the reaction mix comprises nucleoside monophosphates. Claims 10 and 11 limit the template for synthesizing the biological macromolecules. Claims 12 and 11 limit the reaction to

a batch or continuous reaction respectively. Claims 14 and 15 limit the E. coli extract comprising the reaction mix. Claims 16 limits the reaction mix to a magnesium concentration to about 5 mM to 10 mM. Claim 18 limits that the reaction mix comprises one or more of spermine, spermidine and putrescine.

Claim 19 contains the wherein clause that the "reaction mixture yields 400 μg/mL of synthesized polypeptide".

M.P.E.P 2111.04 state:

> Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure

Furthermore since this is a method claim, patentability lies in the active steps. Prior art methods reading on all the active steps will inherently have the same results and physical properties (M.P.E.P 2112.02). Therefore this wherein clause is given little patentable weight since it does not add a further step to the method but only recites an intended result of the method.

Swartz #1 teach a method of synthesizing biological marcomolecules such as proteins (Figures 1 and 3) using a reaction mix comprising:

- 57 mM Hepes-KOH (pH=8.2);
- 1.2 mM ATP;
- 0.85 mM each of GTP, UTP, CTP;
- 1 mM **DTT (dithiothreitol)**;
- 200mM of glutamate;
- the nucleotide monophosphate cAMP,

- **phosphoenol pyruvate (PEP)**,
- 15 mM of $Mg(Ac)_2$ and,
- a T7RNA polymerise to transcribe mRNA from a DNA plasmid for subsequent protein translation using an E. coli S30 extract (col 9, lines 34-41).

E.coli S30 extract is the same bacteria extract described in the Applicant's specification (paragraph 53), therefore is presumed to have all the limitations of claim 14 and 15. Swartz #1 also teach that if pyruvate is used as an energy source then the PEP is removed for the reaction mix and replaced with 32 mM of pyruvate and 6.7 mM of potassium phosphate (col 9, lines 43-48). Swartz #1 teach that a phosphate source is released and recycled during the reaction (Fig 1A and 1B, where "Pi" is the abbreviation for inorganic phosphate). Their method can be performed continuously or batch-wise (col 6, lines 25-30). They also teach their reaction mix can comprise spermine or spermidine (col 6, lines 49-50). Swartz#1 teach that the translation of RNA into polypeptides (Swartz#1, col 6, line 16) specifically the direct translation of mRNA to produce proteins (Swartz#1, col 6, lines 30-40). They teach their protein yield is as high as 700 µg/mL (Swartz#1, Fig 9B).

Concerning claim 17. While Swartz#1 teach polyethylene glycol in their reaction mix they also teach alternatives such as dextran, diethyl aminoethyl, quaternary aminoethyl and aminoethyl (col 6, lines 54-55). M.P.E.P. § 2173.05(i) states "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims". Therefore since Swarz#1 teach an alternative to polyethylene glycol then it would be obvious to exclude it via substituting it for another listed compound since they are known for the same purpose (M.P.E.P. § 2144.06).

Swartz#1 clearly teach the use of the exogenous nucleoside triphosphate, ATP as the energy source for translation and transcription. However it would be obvious to one of ordinary skill in the art from the teachings of Swartz#1 that ADP can replace ATP as an alternate energy source. Swartz#1 clearly teach that ATP is required for the ADP/ATP redox cycle which mediates the energy for the protein translation (Swartz#1, Figure 1). However since this ADP/ATP is a cyclic reaction then one of ordinary skill in the art would recognize by looking at Figure 1 of Swartz#1 that ATP can be generated by the reaction of pyruvate kinase with ADP as the starting material. This reaction would generate ATP that is recycled back to ADP via the translation process as shown in the diagram of Fig 1A of Swartz#1 which is copied below.

FIG. 1A

Therefore one of ordinary skill in the art would recognize that ADP could be substituted for ATP in the starting reaction mix and protein translation would still occur based on ATP being generated by the reaction of the pyruvate kinase and ADP. A simple substitution one known element (ADP) for another (ATP) is obvious when both will predictably lead to the same result (protein translation) (KSR Int'l Co. v. Teleflex, Inc. 550 U.S. 398 (2007), Section A, pg 14). Therefore it would be obvious for one of ordinary skill in the art to remove the exogenous nucleoside triphosphate, ATP from the system.

Swartz#1 also teach the use of the other nucleotide triphosphates GTP, UTP, CTP and ATP as substrates to transcribe the DNA template to RNA (Swartz, col 9, 35-40). Swartz#1

does not teach the use of nucleotide monophosphates for transcription. However it would be obvious to substitute these NTPs for their respective **nucleotide monophosphates (NMPs)** from the teachings of Schulte et al.

Schulte et al. teach a method that converts NMPs to NTPs for in vitro synthesis of nucleic acid molecules (Schulte, paragraph 11) such as mRNA from a DNA template (paragraph 18). Schulte et al. teach that substituting NMPs for NTPs in their method has significant cost savings as well (Schulte, paragraph 16). They explicitly state that this method is to be used in the transcription and translation for protein synthesis with cell extracts (Schulte, paragraph 18). Schulte et al. even teach that amount of ATP required to provide energy for this synthesis can be generated by pyruvate kinase (Schulte, paragraph 20) like Swartz#1.

Therefore it would have been obvious to one of ordinary skill in the art to use the method of Schulte et al. to substitute NMPs for NTPs in the transcription and translation of protein in the cell extract of Swartz#1. The motivation and reasonable expectation of success is provided by Schulte et al. who expressly teach that this is the purpose of the invention (Schulte paragraphs 18 and 19). Furthermore one of ordinary skill in the art would recognize Schulte et al. as a known mRNA synthesis technique to improve the transcription step of the method of Swartz#1 by lowering the cost of the starting materials (KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007) pg 13).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

Claims 1-6 and 10-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Swartz#2 (U.S. Patent # 6337191, issued 2002, cited in PTO-892, 9/22/10) in view of Schulte et al. (U.S. Patent Application # 2003/0113778, priority date 10/30/01).

These claims are drawn to a method of synthesizing polynucleotides and/or polypeptides in a cell-free reaction mix comprising:

- Bacterial cell extract;
- A template for the production of the polynucleotides and/or polypeptide;
- Monomers for the polynucleotides and/or polypeptides to be synthesized;
- Cofactors, enzymes and other reagents necessary for synthesis;
- At least 10mM of a phosphate free energy source that may include glucose, glutamate or pyruvate;
- Absence of exogenous NTPs;
- At least 1mM of exogenous phosphate that is provided by potassium phosphate, magnesium phosphate or ammonium phosphate.

The phosphates such as potassium phosphate are further limited to a concentration of 1 mM to about 20 mM. Claim 7 limits that the phosphate source is released during the reaction. Claim 8 limits that the reaction mix comprises nucleoside monophosphates. Claims 10 and 11 limit the template for synthesizing the biological macromolecules. Claims 12 and 11 limit the reaction to a batch or continuous reaction respectively. Claims 14 and 15 limit the E. coli extract comprising the reaction mix. Claims 16 limits the reaction mix to a magnesium concentration to

about 5 mM to 10 mM. Claim 18 limits that the reaction mix comprises one or more of spermine, spermidine and putrescine.

Claim 19 contains the wherein clause that the "reaction mixture yields 400 μg/mL of synthesized polypeptide".

M.P.E.P 2111.04 state:

> Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure

Furthermore since this is a method claim, patentability lies in the active steps. Prior art methods reading on all the active steps will inherently have the same results and physical properties (M.P.E.P 2112.02). Therefore this wherein clause is given little patentable weight since it does not add a further step to the method but only recites an intended result of the method.

Swartz #2 teach a method of synthesizing biological marcomolecules such as proteins (Example 2) using a reaction mix comprising:

- 57 mM Hepes-KOH (pH=8.2);
- 1.2 mM ATP;
- 0.85 mM each of GTP, UTP, CTP;
- 1 mM **DTT** (**dithiothreitol**);
- 200mM of glutamate;
- the nucletide monophosphate cAMP,
- **phosphoenol pyruvate** (**PEP**),
- 15 mM of $Mg(Ac)_2$ and,

- a T7RNA polymerise to transcribe mRNA from a DNA plasmid for subsequent protein translation using an E. coli S30 extract.

The E. coli S30 extract which is the same bacterial extract describe in the Applicant's (paragraph 53) therefore is presumed to have all the limitations of claim 14 and 15. Swartz #2 also teach that if pyruvate is used as an energy source then the PEP is removed for the reaction mix and replaced with 33 mM of pyruvate and 6.7 mM of potassium phosphate (col 9, lines 43-48). Swartz #2 teach that other energy sources such as glucose can be used as well (col 2, lines 55-60). Swartz #2 teach that a phosphate source is released and recycled during the reaction (col 4, lines 1-5). Their method can be performed continuously or batch-wise (col 5, lines 50-52). They also teach their reaction mix can comprise spermine or spermidine (col 8, lines 18-19). They teach that their protein yield is as high as 513 μg/mL (Example 4).

Concerning claim 17. While Swartz#2 teach the polyethylene glycol, PEG 8000, (Example 2) in their reaction mix, they also teach alternatives such as dextran, diethyl aminoethyl, quaternary aminoethyl and aminoethyl (col 8, lines 20-25). M.P.E.P. § 2173.05(i) states "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims". Therefore since Swarz#2 teach an alternative to polyethylene glycol then it would be obvious to exclude it via substituting it for another listed compound since they are known for the same purpose (M.P.E.P. § 2144.06).

Swartz#2 clearly teach the use of the exogenous nucleoside triphosphate, ATP as the energy source for translation and transcription. However it would be obvious to one of ordinary skill in the art from the teachings of Swartz#2 that ADP can replace ATP. Swartz#2 teach that

ATP can be synthesized from ADP via the glycolytic pathway using glucose, pyruvate or PEP (Swartz#2, col 2, lines 50-60). Swartz#2 teach that an enzymes such as hexokinase (col 4, lines 50-60) or pyruvate oxidase (col 5, lines 30-40) reacts with their respective substrates of glucose or pyruvate and PEP to synthesize ATP from ADP. Therefore one of ordinary skill in the art would recognize that ADP could be substituted for ATP in the starting reaction mix and protein translation would still occur based on ATP/ADP being a reversible and cyclic process. A simple substitution one known element (ADP) for another (ATP) is obvious when both will predictably lead to the same result (protein translation) (KSR Int'l Co. v. Teleflex, Inc. 550 U.S. 398 (2007), Section A, pg 14). Therefore it would be obvious for one of ordinary skill in the art to remove the exogenous nucleoside triphosphate, ATP from the system.

Swartz#2 also teach the use of the other nucleotide triphosphates GTP, UTP, CTP and ATP as substrates to transcribe the DNA template to RNA (Example 2). Swartz#2 does not teach the use of nucleotide monophosphates for transcription. However it would be obvious to substitute these NTPs for their respective **nucleotide monophosphates (NMPs)** from the teachings of Schulte et al.

Schulte et al. teach a method that converts NMPs to NTPs for in vitro synthesis of nucleic acid molecules (Schulte, paragraph 11) such as mRNA from a DNA template (paragraph 18). Schulte et al. teach that substituting NMPs for NTPs in their method has significant cost savings as well (Schulte, paragraph 16). They explicitly state that this method is to be used in the transcription and translation for protein synthesis with cell extracts (Schulte, paragraph 18). Schulte et al. even teach that amount of ATP required to provide energy for this synthesis can be generated by pyruvate kinase (Schulte, paragraph 20) like Swartz#2.

Therefore it would have been obvious to one of ordinary skill in the art to use the method of Schulte et al. to substitute NMPs for NTPs in the transcription and translation of protein in the cell extract of Swartz#2. The motivation and reasonable expectation of success is provided by Schulte et al. who expressly teach that this is the purpose of the invention (Schulte paragraphs 18 and 19). Furthermore one of ordinary skill in the art would recognize Schulte et al. as a known mRNA synthesis technique as an improved transcription step to the method of Swartz#2 by lowering the cost of the starting materials (KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007) pg 13).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowable or free of the art.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicant argues the anticipation rejections. However, these rejections are no longer maintained and are replaced by obviousness rejections,.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
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/Irene Marx/
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